(FORM PTO-1390 (Modified) (REV 11-2000)) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **215246US0PCT**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): **09/926411**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/02756	**26 April 2000**	**30 April 1999**

TITLE OF INVENTION
AGENT FOR TREATING DRY EYE

APPLICANT(S) FOR DO/EO/US
UENO Ruyji

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report
Request for Priority Under 35 U.S.C 119(e)
PCT/IB/304
PCT/IB/308

U.S. APPLICATION No. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/926411	PCT/JP00/02756	215246US0PCT

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		CALCULATIONS PTO USE ONLY
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1040.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$890.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$740.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$710.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$890.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	7 - 20 =	0	x $18.00	$0.00
Independent claims	3 - 3 =	0	x $84.00	$0.00
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00
TOTAL OF ABOVE CALCULATIONS =				$890.00
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				$0.00
SUBTOTAL =				$890.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$0.00
TOTAL NATIONAL FEE =				$890.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				$0.00
TOTAL FEES ENCLOSED =				$890.00
			Amount to be: refunded	$
			charged	$

a. ☒ A check in the amount of **$890.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Surinder Sachar
Registration No. 34,423

22850

Surinder Sachar
SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

Oct 29 2001
DATE

215246US-0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :

RYUJI UENO :

SERIAL NO: NEW U.S. PCT APPLN. : ATTN: APPLICATION BRANCH
(Based on PCT/JP00/02756)

FILED: HEREWITH :

FOR: AGENT FOR TREATING DRY EYE

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE SPECIFICATION

Please replace the title on page 1, line 1 with the following:

--USE OF MACROLIDE COMPOUNDS FOR THE TREATMENT OF DRY EYE--.

Please delete the paragraph beginning on page 6, lines 17-19 and replace with the following paragraph.

acyl such as aliphatic acyl, aromatic acyl and aliphatic acyl substituted by aromatic group, which are derived from carboxylic acid, sulfonic acid and carbamic acid; and the like.

IN THE CLAIMS

Please amend the claims as shown on the marked-up copy following this amendment to read as follows.

3. (Amended) The agent of claim 1, wherein the macrolide compound is FK506.

4. (Amended) The agent of claim 1, which is in the form of a preparation for local administration to the eye.

5. (Amended) The agent of claim 1, which aims at improving tear film breakup time.

REMARKS

Claims 1-7 are active in the present application. Claims 2-5 have been amended to remove multiple dependencies. The specification has been amended to correct a typographical or clerical error. No new matter is believed to have been added. An action on the merits and allowance of claims is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

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Marked-Up Copy
Serial No:

Amendment Filed on:
10-29-01

IN THE SPECIFICATION

Please replace the title on page 1, with the following:

[OLD TITLE] NEW TITLE

Please delete the paragraph beginning on page 6, lines 17-19 and replace with the following paragraph.

--acyl such as aliphatic acyl [derived from carboxylic acid, sulfonic acid and carbamic acid, aromatic acyl, and aliphatic acyl substituted by aromatic group], aromatic acyl and aliphatic acyl substituted by aromatic group, which are derived from carboxylic acid, sulfonic acid and carbamic acid; and the like.--

IN THE CLAIMS

Please amend the claims as follows.

--3. (Amended) The agent of claim 1 [or claim 2], wherein the macrolide compound is FK506.

4. (Amended) The agent of [any of claim 1 to claim 3] claim 1, which is in the form of a preparation for local administration to the eye.

5. (Amended) The agent of [any of claim 1 to claim 4] claim 1, which aims at improving tear film breakup time.--

SPECIFICATION

AGENT FOR TREATING DRY EYE

Technical Field

The present invention relates to an agent for treating a dry eye.

Background Art

One of the symptoms of ophthalmic diseases drawing much attention these days is dry eye. The dry eye is defined to mean a condition wherein lacrimal fluid is less in amount or abnormal in quality, with or without the presence of corneal and conjunctival lesion (Yamada, M. et al., Folia Ophthalmol. Jpn., 43, 1289-1293 (1992)). Specific symptoms include dry eye observed in hypolacrimation, alacrima, xerophthalmia, Sjögren syndrome, keratoconjunctivitis sicca, Stevens-Johnson syndrome, ocular pemphigoid, marginal blepharitis, diabetes and the like, dry eye observed after cataract operation, dry eye in conjunction with allergic conjunctivitis and the like, and dry eye due to hypolacrimation caused by increased VDT (visual display terminal) work, dry room with air conditioning and the like.

The dry eye is caused by various factors that may not be entirely clear, and, at the moment, a drastic treatment method, such as promotion of the secretion of lacrimal fluid, has not been established yet. Therefore, the dry eye has been diagnosed according to the subjective symptoms obtained by questioning and objective symptoms known from lacrimal fluid evaluation tests (tear film breakup time, Schirmer test, lacrimal fluid clearance test and the like), corneal and conjunctival staining tests (fluorescein staining, rose bengale staining and the like), and the like. For example, tear film breakup time (BUT), which is one of the lacrimal fluid evaluation tests, reflects the stability of precorneal tear film, and means the time (sec) from complete nictitation to the initial breakage of the precorneal tear film. A lower BUT means severer dry eye symptom. In the case of severe dry eye, the breakage of the tear film occurs immediately after nictitation, which is rated as BUT zero (0) sec.

At present, a dry eye therapy includes increasing lacrimal fluid reservoir in conjunctival sac by instillation of artificial tears to alleviate the subjective symptoms of patients or to protect the eye from drying, and other methods.

For the above-mentioned therapy, instillation of chondroitin

sulfate, methyl cellulose and the like, and internal use of bromhexine hydrochloride, salivary gland hormone and the like have been the typical methods. However, the effect of such therapy is not necessarily satisfactory. While instillation of artificial tears and use of a goggle eye patch and the like have been the means to protect the eyes from drying, these are not more than auxiliary therapy methods.

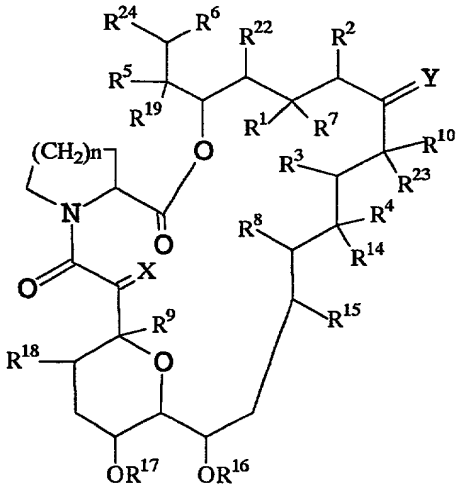
DISCLOSURE OF THE INVENTION

As a result of the intensive studies done by the present inventor, it was surprisingly found that a macrolide compound has a superior improving effect on dry eye symptoms, particularly subjective symptoms, and in lacrimal fluid evaluation tests, such as tear film breakup time and the like, and exhibits a superior therapeutic effect on the dry eye, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

(1) An agent for treating a dry eye, comprising a macrolide compound as an active ingredient.

(2) The agent of (1), wherein the macrolide compound is a tricyclo compound (I) of the following formula



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pair ;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may

form oxo with R^1 ;

R^8 and R^9 each independently show hydrogen atom or hydroxy ;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo ;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl ;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl ;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s) ; and

n is 1 or 2.

In addition to the meaning noted above, Y, R^{10} and R^{23} may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy,

or a pharmaceutically acceptable salt thereof.

(3) The agent of (1) or (2), wherein the macrolide compound is FK506.

(4) The agent of any of (1) to (3), which is in the form of a preparation for local administration to the eye.

(5) The agent of any of (1) to (4), which aims at improving the tear film breakup time.

(6) A method for treating dry eye, comprising administering an effective amount of a macrolide compound to a subject in need of the treatment of dry eye.

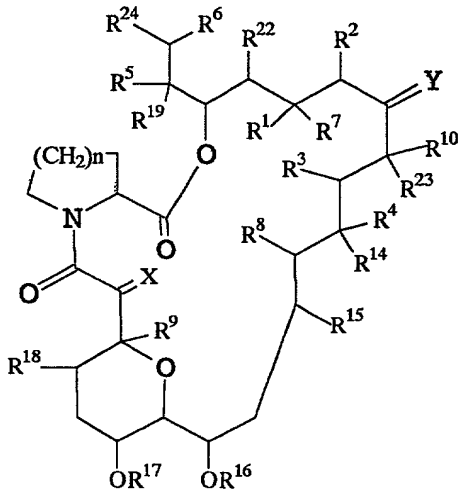
(7) Use of a macrolide compound for the production of a pharmaceutical composition for the treatment of dry eye.

DETAILED DESCRIPTION OF THE INVENTION

Some of the macrolide compounds to be used in the present invention are known as shown below and a novel macrolide compound can be prepared from these known macrolide compounds by a known method. Preferable examples thereof include macrolide compounds such as FK506, Ascomycin

derivative, Rapamycin derivative and the like.

Specific examples of macrolide compound include tricyclo compound (I) of the following formula and a pharmaceutically acceptable salt thereof.



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pair;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2.

In addition to the meaning noted above, Y, R^{10} and R^{23} may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy.

Preferable R^{24} is, for example, cyclo(C_5-C_7)alkyl optionally having suitable substituent, such as the following.

(a) 3,4-dioxocyclohexyl,

(b) 3-R^{20}-4-R^{21}-cyclohexyl,

wherein R^{20} is hydroxy, alkyloxy or $-OCH_2OCH_2CH_2OCH_3$, and R^{21} is hydroxy, -OCN, alkyloxy, heteroaryloxy optionally having suitable substituent, $-OCH_2OCH_2CH_2OCH_3$, protected hydroxy, chloro, bromo, iodo, aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO-$ (wherein R^{25} is hydroxy optionally protected where desired or protected amino, and R^{26} is hydrogen atom or methyl),

or R^{20} and R^{21} in combination form an oxygen atom of epoxide ring, and

(c) cyclopentyl substituted by methoxymethyl, protected hydroxymethyl where desired, acyloxymethyl (wherein acyl moiety is optionally quaternized dimethylamino where desired or optionally esterified carboxy), one or more optionally protected amino and/or hydroxy, or aminooxalyloxymethyl. Preferable example includes 2-formyl-cyclopentyl.

The definition of each symbol used in the formula (I), specific examples thereof and preferable embodiments thereof are explained in detail in the following.

"Lower" means that a group has 1 to 6 carbon atoms unless otherwise indicated.

Preferable examples of "alkyl" and the alkyl moiety of "alkyloxy" include linear or branched aliphatic hydrocarbon residue, such as lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl and the like).

Preferable examples of "alkenyl" include linear or branched aliphatic hydrocarbon residue having one double bond, such as lower alkenyl (e.g., vinyl, propenyl (e.g., allyl and the like), butenyl, methylpropenyl, pentenyl, hexenyl and the like).

Preferable examples of "aryl" include phenyl, tolyl, xylyl,

cumenyl, mesityl, naphthyl and the like.

Preferable examples of the protective group of "protected hydroxy" and "protected amino" include 1-(lower alkylthio)(lower)alkyl such as lower alkylthiomethyl (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl and the like), with more preference given to C_1 - C_4 alkylthiomethyl and most preference given to methylthiomethyl;

tri-substituted silyl such as tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl and the like), and lower alkyldiarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl and the like, with more preference given to tri(C_1-C_4)alkylsilyl and C_1-C_4 alkyldiphenylsilyl, and most preference given to tert-butyldimethylsilyl, tert-butyldiphenylsilyl;

acyl such as aliphatic acyl derived from carboxylic acid, sulfonic acid and carbamic acid, aromatic acyl, and aliphatic acyl substituted by aromatic group; and the like.

The aliphatic acyl is exemplified by lower alkanoyl optionally having one or more suitable substituent(s) (e.g., carboxy) such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl and the like;

cyclo(lower)alkyloxy(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower alkyl) such as cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, mentyloxyacetyl, mentyloxypropionyl, mentyloxybutyryl, mentyloxypentanoyl, mentyloxyhexanoyl and the like, camphorsulfonyl;

lower alkylcarbamoyl having one or more suitable substituent(s) such as carboxy or protected carboxy and the like, such as carboxy(lower)alkylcarbamoyl (e.g., carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl) and

tri(lower)alkylsilyl(lower)alkyloxycarbonyl(lower)-alkylcarbamoyl (e.g., trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl,

triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl); and the like.

Aromatic acyl is exemplified by aroyl optionally having suitable substituent(s) (e.g., nitro), such as benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl and the like; and arenesulfonyl optionally having one or more suitable substituent(s) (e.g., halogen), such as benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl and the like.

The aliphatic acyl substituted by aromatic group may be, for example, ar(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower alkyloxy or trihalo(lower)alkyl and the like), wherein specific examples are phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl and the like.

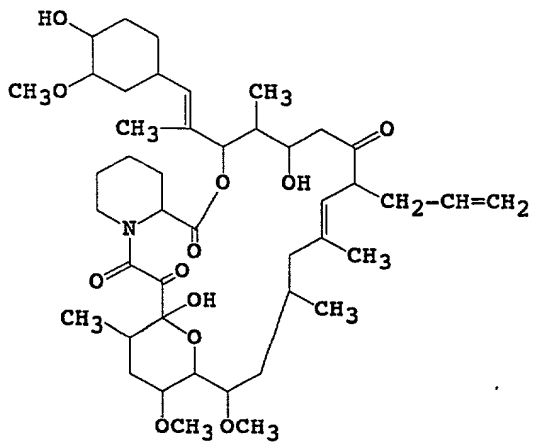
Of the above-mentiond acyl, more preferable acyl includes C_1 - C_4 alkanoyl optionally having carboxy, cyclo(C_5 - C_6)alkyloxy(C_1 - C_4)alkanoyl having two (C_1 - C_4)alkyl in the cycloalkyl moiety, camphorsulfonyl, carboxy (C_1 - C_4)alkylcarbamoyl, tri(C_1 - C_4)alkylsilyl(C_1 - C_4)alkyloxycarbonyl(C_1 - C_4)alkylcarbamoyl, benzoyl optionally having 1 or 2 nitro groups, benzenesulfonyl having halogen, and phenyl(C_1 - C_4)alkanoyl having C_1 - C_4 alkyloxy and trihalo(C_1 - C_4)alkyl. Of these, most preferred are acetyl, carboxypropionyl, mentyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl and the like.

Preferable examples of the "heterocyclic group consisting of saturated or unsaturated 5 or 6-membered ring having nitrogen atom, sulfur atom and/or oxygen atom" are pyrolyl, tetrahydrofuryl and the like.

The "heteroaryl optionally having a suitable substituent" moiety of the "heteroaryloxy optionally having a suitable substituent" is that exemplified for R^1 of the compound of the formula I of EP-A-532,088, with preference given to 1-hydroxyethylindol-5-yl. This publication is incorporated hereinto by reference.

The tricyclo compound (I) and a pharmaceutically acceptable salt thereof to be used in the present invention have immunosuppressive action, antibacterial action and other pharmacological activity, so that they are useful for the prophylaxis and treatment of rejection in organ or tissue transplantation, graft versus host reaction, autoimmune diseases, infectious diseases and the like, as noted, together with the production method thereof, in, for example, EP-A-184162, EP-A-323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059 and the like, all of these publications are hereby incorporated by reference.

In particular, the compounds called FR900506 (=FK506), FR900520 (Ascomycin), FR900523 and FR900525 are produced by the genus *Streptomyces*, such as *Streptomyces tsukubaensis*, No. 9993 (depository : National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology, the Ministry of International Trade and Industry, 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly : Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit : October 5, 1984, deposit number : FERMBP-927) or *Streptomyces hygroscopicus subsp. Yakushimaensis*, No. 7238 (depository : National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology, 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly : Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit : January 12, 1985, deposit number : FERM BP-928 (EP-A-0184162)). The compound of the following formula, FK506 (general name : Tacrolimus), is a representative compound.



Chemical name : 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

Of the tricyclo compounds (I), more preferred is a compound wherein adjacent pairs of R^3 and R^4, and R^5 and R^6 each independently form another bond between carbon atoms binding with the members of each pair ;

R^8 and R^{23} each independently show hydrogen atom ;

R^9 is hydroxy ;

R^{10} is methyl, ethyl, propyl or allyl ;

X is (hydrogen atom, hydrogen atom) or oxo ;

Y is oxo ;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{22} each independently show methyl ;

R^{24} is 3-R^{20}-4-R^{21}-cyclohexyl,

wherein R^{20} is hydroxy, alkyloxy or $-OCH_2OCH_2CH_2OCH_3$, and

R^{21} is hydroxy, -OCN, alkyloxy, heteroaryloxy optionally having suitable substituent, $-OCH_2OCH_2CH_2OCH_3$, protected hydroxy, chloro, bromo, iodo, aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy or $R^{25}R^{26}CHCOO-$ (wherein R^{25} is hydroxy optionally protected where desired, or protected amino, and R^{26} is hydrogen atom or methyl), or R^{20} and R^{21} in combination form an oxygen atom of epoxide ring; and

n is 1 or 2.

Particularly preferable tricyclo compound (I) includes, besides FK506, Ascomycin derivatives such as halogenated derivative of 33-epi-chloro-33-desoxy Ascomycin described in Example 66a of

EP-A-427,680 and the like.

Other preferable macrolide compounds include Rapamycin described in MERCK INDEX, 12 edition, No. 8288 and derivatives thereof. Preferable examples thereof include O-substituted derivative described at page 1 of WO95/16691, formula A, wherein the 40th hydroxy is -OR_1 (wherein R_1 is hydroxyalkyl, hydroalkyloxyalkyl, acylaminoalkyl or aminoalkyl), such as 40-O-(2-hydroxy)ethyl Rapamycin, 40-O-(3-hydroxy)propyl Rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl Rapamycin and 40-O-(2-acetaminoethyl) Rapamycin. These O-substituted derivatives can be produced by reacting, under appropriate conditions, Rapamycin (or dihydro or deoxo Rapamycin) and an organic radical bound with a leaving group (e.g., RX wherein R is an organic radical desirable as O-substituent, such as alkyl, allyl and benzyl moiety, and X is a leaving group such as $CCl_3C(NH)O$ and CF_3SO_3)). The conditions are: when X is $CCl_3C(NH)O$, acidic or neutral conditions, such as in the presence of trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their corresponding pyridinium or substituted pyridinium salt, and when X is CF_3SO_3, in the presence of a base such as pyridine, substituted pyridine, diisopropylethylamine and pentamethylpiperidine. The most preferable Rapamycin derivative is 40-O-(2-hydroxy)ethyl Rapamycin as disclosed in WO94/09010. The contents of the above references are hereby incorporated into the specification by reference.

The pharmaceutically acceptable salt of tricyclo compound (I), Rapamycin and derivatives thereof are nontoxic and pharmaceutically acceptable conventional salts, which are exemplified by salts with inorganic or organic base such as alkali metal salt (e.g., sodium salt, potassium salt and the like), alkaline earth metal salt (e.g., calcium salt, magnesium salt and the like), ammonium salt, and amine salt (e.g., triethylamine salt, N-benzyl-N-methylamine salt and the like).

In the macrolide compound of the present invention, conformer or one or more pairs of stereoisomers, such as optical isomers and geometric isomers, may be included due to asymmetric carbon atom and double bond. Such conformers and isomers are also encompassed in the present invention. In addition, macrolide compounds can form solvates, which case is also encompassed in the present invention. Preferable solvate is exemplified by hydrates and ethanolates.

The diseases associated with dry eye in the present invention

include those mentioned above inclusive of hypolacrimation, alacrima xerophthalmia, Sjögren syndrome, keratoconjunctivitis sicca, Stevens-Johnson syndrome, ocular pemphigoid, marginal blepharitis, diabetes and the like, dry eye observed after cataract operation, that in conjunction with allergic conjunctivitis and the like. The dry eye similar to hypolacrimatioin is also observed, which is caused by VDT work and dry room due to air conditioning and the like.

The treatment agent of the present invention is effective against the above-mentioned dry eye and for the improvement of subjective symptoms, particularly dry eye, and in evaluation of tears, such as tear film breakup time (BUT) and the like.

The treatment in the context of the present invention includes any management such as prevention, cure, alleviation of symptom, reduction of symptom, prevention of progression and the like.

The macrolide compound to be used in the present invention can be used as a pharmaceutical agent for human and animals, and can be administered systemically or locally by oral administration, intravenous administration (inclusive of transfusion), subcutaneous administration, rectal or virginal administration, administration to local site in the eye (inclusive of eye ointment). In consideration of systemic influence, significant expression of the effect and the like, it is particularly preferably used in the form for local administration to the eye.

The dose of the macrolide compound varies depending on the kind, age, body weight of the administration subject such as human and animal, conditions to be treated, desired therapeutic effect, administration method, treatment period and the like. Generally, when it is administered systemically, the dose is about 0.0001 - 1000 mg, preferably 0.001 - 500 mg, which is given in a single dose or 2 to 4 dividual doses a day or administered in a sustained manner. When it is administered locally to the eye, a preparation containing the active ingredient in a proportion of 0.001 - 10.0 w/v%, preferably 0.005 - 5.0 w/v%, is applied to one eye several times a day, preferably instilled or applied 1 to 6 times a day.

According to the present invention, a macrolide compound, which is an active ingredient, can be administered alone or in combination with other pharmacologically active components. When administered after formulating a preparation, it can be administered as a preparation

produced by a conventional method. The dosage form may be, for example, eye drop, eye ointment, powder, granule, tablet, capsule, injection, ointment and the like, with particular preference given to eye drop and eye ointment. Such preparation can be produced according to a conventional method. Of such preparations, an oral preparation is preferably a solid solution preparation produced in the same manner as in the preparation of EP-A-0240773. When an eye drop is desired, an eye drop as described in EP-A-0406791 is preferable. When desired, additives generally used for eye drop, such as isotonizing agent (e.g., sodium chloride), buffering agent (e.g., boric acid, disodium hydrogenphosphate, sodium dihydrogenphosphate and the like), preservative (e.g., benzalkonium chloride, benzetonium chloride, chlorobutanol and the like), tackifier [e.g., sugar (lactose, mannitol, maltose and the like), hyaluronic acid or salt thereof (sodium hyaluronate, potassium hyaluronate and the like), mucopolysaccharide (e.g., chondroitin sulfate and the like), sodium polyacrylate, carboxy vinyl polymer, crosslinked polyacrylate, and the like] may be added. The contents of the above references in this respect are hereby incorporated into the specification by reference.

The present invention is explained in more detail in the following by referring to Examples. The present invention is not limited to these examples.

Examples

Example 1

Using FK506 as the active ingredient in the present invention, a 0.06% eye drop (suspension) having the following formulation was used as a test drug.

Test drug

A suspension having the following formulation was produced in the same manner as in EP-A-0406791 (Example 6).

FK506	0.6 mg
polyvinyl alcohol	7.0 mg
disodium hydrogenphosphate 12 hydrate	0.05 mg
sodium dihydrogenphosphate 2 hydrate	0.76 mg
phosphoric acid	appropriate amount
sodium hydroxide	appropriate amount
sodium chloride	8.56 mg
benzalkonium chloride	0.1 mg
injectable water	appropriate amount
Total amount	1 ml

The above-mentioned test drug was consecutively administered twice a day for two weeks to a male (44 years old) having subjective symptoms of dry eye (sense of dryness, foreign body and grittiness) and, as a result, the subjective symptoms disappeared.

From the above result, the test drug was confirmed to be effective for the improvement of subjective symptoms of dry eye.

Example 2

A suspension having the same formulation as in Example 1 was produced using FK506 as the active ingredient to give a 0.01% FK506 eye drop (suspension) and 0.1% FK506 eye drop (suspension) as test drugs. The base for the eye drops was used as the control drug.

The above-mentioned test drugs and the control drug were instilled four times a day for 7 days to 18 healthy subjects (6 per group) at 8:00, 11:00, 14:00 and 17:00.

The tear film breakup time (sec) of the right eye was measured before instillation and 8 days after instillation. The difference between before and after the instillation was calculated, and taken as the mean variation of the tear film breakup time.

The tear film breakup time was measured according to the conventional method. After instillation of fluorescein, the tear film was formed on the surface of the eye by nictitation. The surface of the eye was observed with a microscope without allowing nictitation, and the time until breakage of the tear film (burst by surface tension) was measured. The results are shown in Table 1.

Table 1

Group	Mean variation of tear film breakup time (sec)
Control drug group	+0.17
0.01% FK506 eye drop group	+0.58
0.1% FK506 eye drop group	+0.75

From the above results, the test drug was confirmed to be effective for the improvement of the tear film breakup time, which is one of the tests for lacrimal fluid evaluation of dry eye.

Industrial applicability

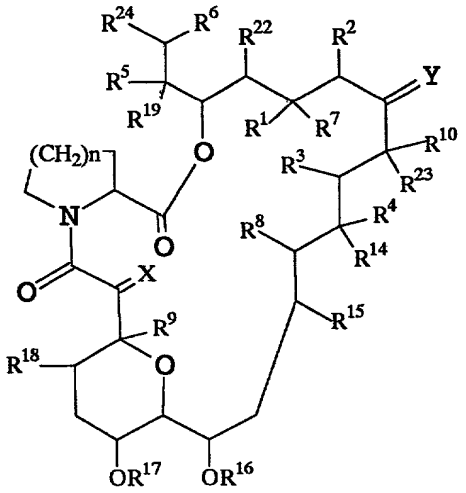
The treatment agent of the present invention, which comprises a macrolide compound as an active ingredient, has a superior improving effect on dry eye, particularly subjective symptom of dry eye and in lacrimal fluid evaluation such as tear film breakup time and the like. Therefore, the treatment agent of the present invention is suggested to be useful as an agent for treating dry eye.

This application is based on application No. 60/132,009 filed in United States of America, the content of which is incorporated hereinto by reference.

CLAIMS

1. An agent for treating a dry eye, comprising a macrolide compound as an active ingredient.

2. The agent of claim 1, wherein the macrolide compound is a tricyclo compound (I) of the following formula



(I)

wherein

adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pair;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen

atom or alkyl;

R^{24} is an optionally substituted ring which optionally contains one or more hetero atom(s); and

n is 1 or 2,

wherein

Y, R^{10} and R^{23} optionally form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy,

or a pharmaceutically acceptable salt thereof.

3. The agent of claim 1 or claim 2, wherein the macrolide compound is FK506.

4. The agent of any of claim 1 to claim 3, which is in the form of a preparation for local administration to the eye.

5. The agent of any of claim 1 to claim 4, which aims at improving tear film breakup time.

6. A method for treating a dry eye, comprising administering an effective amount of a macrolide compound to a subject in need of the treatment of dry eye.

7. Use of a macrolide compound for the production of a pharmaceutical composition for the treatment of dry eye.

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

60/132,009	April 30,1999
(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)
PCT/JP00/02756	April 26, 2000	pending

And we (I) hereby appoint: Norman F. Oblon, Registration Number 24,618; Marvin J. Spivak, Registration Number 24,913; C. Irvin McClelland, Registration Number 21,124; Gregory J. Maier, Registration Number 25,599; Arthur I. Neustadt, Registration Number 24,854; Richard D. Kelly, Registration Number 27,757; James D. Hamilton, Registration Number 28,421; Eckhard H. Kuesters, Registration Number 28,870; Robert T. Pous, Registration Number 29,099; Charles L. Gholz, Registration Number 26,395; Vincent J. Sunderdick, Registration Number 29,004; William E. Beaumont, Registration Number 30,996; Steven B. Kelber, Registration Number 30,073; Robert F. Gnuse, Registration Number 27,295; Jean-Paul Lavalleye, Registration Number 31,451; Timothy R. Schwart, Registration Number 32,171; Stephen G. Baxter, Registration Number 32,884; Martin M. Zoltick, Registration Number 35,745; Robert W. Hahl, Registration Number 33,893; Richard L. Treanor, Registration Number 36,379; Steven P. Weihrouch, Registration Number 32,829; John T. Goolkasian, Registration Number 26,142; Marc R. Labgold, Registration Number 34,651; William J. Healey, Registration Number 36,160; Richard L. Chinn, Registration Number 34,305; Steven E. Lipman, Registration Number 30,011; Carl E. Schlier, Registration Number 34,426; James J. Kulbaski, Registration Number 34,648; Catherine B. Richardson, Registration Number 39,007; Richard A. Neifeld, Registration Number 35,299; J. Derek Mason, Registration Number 35,270; and Jacques M. Dulin, Registration Number 24,067; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Tide 18 of the United States Code and that such willfull false statements may jeapordize the validity of the application or any patent issuing thereon.

Ryuji UENO
NAME OF FIRST JOINT INVENTOR

Residence: MD, USA

Signature of Inventor

Citizen of: Japan

October 16, 2001
Date

Post Office Address: 11025 Stanmore Drive, Potomac, Montgomery, MD 20854 United States of America

Declaration, Power of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

USE OF MACROLIDE COMPOUNDS FOR THE TREATMENT OF DRY EYE

the specification of which

☐ is attached hereto.
☐ was filed on _____ as
Application Serial No. _____
and amended on _____ .
☒ was filed as PCT international application
Number PCT/JP00/02756
on April 26, 2000,
and was amended under PCT Article 19
on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 1 19(a)-(d) or § 365(b,) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
_____	_____	_____	☐ Yes ☐No
_____	_____	_____	☐ Yes ☐No
_____	_____	_____	☐ Yes ☐No
_____	_____	_____	☐ Yes ☐No